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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,220	11/09/2001	Che-Kun James Shen	514162000120	5165

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,220	SHEN, CHE-KUN JAMES	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and Dr. Shen's declaration filed on 4/17/06 has been acknowledged.

Claims 21-34 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/17/06 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response filed on 05/10/04 the applicant amended the claim 21 to recite claim new limitation "chromosomally integrated". There is no support such claim limitation the speciation as filed. As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). So instant claims encompasses apparently a new matter. No pages or place in the specification was cited to support this amendment. A careful review by the examiner of the specification failed to identify any support for this new limitation. Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21, 23-27 and 30-32 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record on PTO 1449*) in view of Ohtani et al, Nucleic Acids Res. 25;17(4):1589-604, 1989.

The scope of invention as claimed encompasses an isolated cell comprising a transcriptional start site a promoter operably linked to the start site and an enhancer operably linked to the promoter, wherein the enhancer comprises the nucleotide sequences of SEQ ID NO:1. The scope of invention as claimed further encompasses a cell wherein the promoter (ζ–globin promoter) drives the transcription of a polypeptide (growth hormone).

Zhang teaches that HS-40 consists of multiple nuclear factor binding motifs that are occupied *in-vivo* in an erythroid lineage and developmental stage-specific manner. The cited art further teaches systematically analysis and functional roles of these factor-binding motifs of HS-40 by site-directed mutagenesis and transient expression assay in erythroid cell cultures. The cited art teaches that three of these HS-40 enhancer motifs, 5`NF-E2/AP1, GT II, and GATA-1(c), positively regulate the ζ-globin promoter activity in embryonic/fetal erythroid K562 cells and the adult α-globin promoter activity in adult erythroid MEL cells. The cited art further teaches that on the other hand, the 3`NF-E2/AP1 motif is able to exert both positive and negative regulatory effects on the ζ -globin promoter activity in K562 cells, and this dual function appears to be modulated through differential binding of the ubiquitous AP1 factors and the erythroid-enriched NF-E2 factor (page 8561, abstract). The cited art further teaches an expression vector comprising, a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). The cited art further teaches transfection of at least 10^7 host cell using at least 10μg of plasmid construct that inherently incorporated 5-15 copies of transgene after culturing the cells for at least 5 days (page 8502, col.2 para 2). The cited art further teaches a HS-40 enhancer element (NF-E2/AP1-II) which comprises the nucleotide sequence of SEQ ID NO:1 (**tctgagtca**) see page 8503, fig-1B, 3'NF-E2/AP1-II. The cited art further teaches a method of expressing p-HS40 (3'NF-E2/AP1-II)-ζ597GH expression vector into isolated K562 erythroid cells. The genetically modified K562 cells were transfected with expression vector and the expression of growth hormone was measured by GH assay and/or RNA primer extension assay (page 8503 fig 1 and 2). The cited art further teaches that mutant HS-40 enhancer comprises

a 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca) that exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (page 8502, col.2 para.6; page 8504 fig-3). Thus the cited art clearly anticipate the invention as claimed.

Ohtani et al teaches application of electroporation technique for stable induction of genes into human lymphoid cells. The cited art teaches electrophoration is a suitable method for stable induction of DNA, which can be used for variety of human lymphoid cells (page 1591). The cited art further teaches that the efficiency of stable integration of exogenous DNA into the host genome is proportional to the induction of DNA into cells. The cited art further teaches stable transformation of human lymphoid cell lines by electroporation (page 1601, para.2). The cited art teaches that transfection of human erythroleukemia cell line K562, wherein about one per $2X10^5$ cells were stably transfected (page 1601, para.2). Thus the cited art clearly established that electroporation results in stable transfection of foreign genes into human host cells. In addition, the cited art teaches the use of selectable makers for the isolation of homogeneous cell population that express stably transfected gene (page 1595).

Thus it would have been obvious that the transfected K562 cell preparation of Zhang et al (JBC 270(15):8501-8505, 1995 would had inherently contained cells that were stably transfected with the transgene. One would have a reasonable expectation of success, since Zhang teaches electroporation of at least 10^7 cells which after transfection and culture of 5 days would had contained at least 50 cells stably transfected with the p-HS40 (3'NF-E2/AP1-II)-ζ597GH transgene. In addition it would have been further obvious to modify the transgene of Zhang to incorporate a selectable marked in order to isolate a homogeneous cell population. Thus the invention as claimed is prima facie obvious in view of cited prior art of record, if not anticipated by Zhang (1995).

Claims 22, 28-29 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record on PTO 1449)* as applied to claims 21-27 and 30-32 above, and further in view of Zhang et al

(Mol Cell Biol. 4:2298-308, 1993, *ref of record on PTO 1449*) , for the same reasons of record as set forth in the office action mailed on 05/03/05.

Zhang (1995) is discussed above in detail especially in view of Ohtani et al, Nucleic Acids Res. 25;17(4):1589-604, 1989, which clearly suggest the presence of stably transfected cells after 5 days. Even though Zhang inherently teaches an expression vector comprising a 373 bp fragment of HS40 enhancer region, which contain a mutated HS-40 enhancer element (NF-E2/AP1-II) comprising the nucleotide sequence of SEQ ID NO:1 (**tctgagtca**), Zhang does not teach nucleic acid sequences comprising SEQ ID NO:2 and SEQ ID NO:3 of instant application.

Zhang 1993 teaches a nucleotide sequence for HS-40 enhancer element which matches to the nucleotide sequences of SEQ ID NO:2 and SEQ ID NO:3 (page 2299, fig-1B). The cited art specifically teaches mutated HS-40 enhancer element (NF-E2/AP1) which comprises the nucleotide sequence of SEQ ID NO:1 (page 2304, col.1 fig-7A). In addition the cited art teaches transcriptional activation of human embryonic zeta 2 globin gene and the fetal/adult alpha-globin gene is mediated by erythroid cell-specific and developmental stage-specific nuclear factor-DNA complexes, which form at the enhancer (HS-40) and the globin promoters. Furthermore in view of prior art that teaches genetic modification of human and Hela cells, the transfection of other animal cells is obvious if not anticipated in view of cited prior art of record

Thus it would have been obvious that genetically modified embryonic/fetal erythroid K562 and adult erythroid MEL cells as disclosed by Zhang (1995) inherently comprises an expression vector that contains a **tctgagtca** mutated cited in the HS40 enhancer element of Zhang (1993). Alternatively it would have been obvious to use the flanking regions around the **tctgagtca** element, since HS-40 consists of multiple nuclear factor binding motifs that are occupied *in-vivo* in an erythroid lineage and developmental stage-specific manner. One would have been motivated to include the flanking regions around the **tctgagtca** element in order to regulate erythroid developmental in a stage-specific fashion. One would have a reasonable expectation of success because the genetic modification of HS40 enhancer elements by site directed mutagenesis has been

well known in the art at the time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Response to arguments and Dr. Shen's declaration

Applicant's arguments with respect to claims 21-34 have been considered but are moot in view of the new ground(s) of rejection (above).

Dr. Shen's declaration states that the transfection assay conducted by Zhang et al (1995) were transient transfection assays which does not results in the integration of DNA into host cell genome. The declaration further states that random integration frequency in mammalian cells especially human cells is very low (i.e. one every 10^2-10^4 cells). The declaration further states that Zhang et al (1995) did not perform selection of stably transfected cells using selectable markers.

In addition the applicant argues that applicants are not aware of any art that would support the assertion that a construct in a transient transfection assay in human cells would integrate with sufficient frequency to produce an isolated animal cell as presently claimed. The applicant further argues that Zhang reference teaches transiently transfected cells which would lead to isolated cells having chromosomally integrated transgene as presently claimed. The applicant argues that even if the cells were maintained longer than transient transfection assays as taught in Zhang 1995, the construct might have integrated in small fraction of the cells.

However, applicant's arguments are found not persuasive. Zhang (1995) clearly teaches electroporation of at least 10^7 cells which after transfection would had contained at least 50 stably transfected cells according to Ohtani or at least 10^3-10^5 according to applicant own assertion that only one every 10^2-10^4 cells is transfected. In addition Zhang (1995) allows transfected cells to grow for at least 5 days prior to the examination of transgene activity (see Zhang 1995, page 8502, col.2 para.2), which would have further increase the number of transfected cells upon population doubling.

Furthermore the scope of isolated cells as claimed in the context of instant application encompasses a cell isolated from an animal and not a cell(s) isolated to homogeneity in context to the chromosomal integration of the transgene. Thus given the

broadest reasonable interpretation the cited art clearly anticipate the invention as claimed which inherently teaches isolated animal cells having chromosomal integration of the transgene.

The declaration further states the TCTGAGTCA sequence provides the unexpected characteristic of position independent expression when integrated into genome. The applicant argues that Zhang (1995) would not have predicted that TCTGAGTCA provides a position independent effect as the publication teaches transient transfection assay.

However, applicant's arguments are found not persuasive because invention as claimed is not limited to any position independent expression as asserted by the applicant. However, Zhang (1995) teaches the evaluation of transgene activity after 5 days which is sufficient enough to evaluate any position independent expression. In addion position independent activity of the enhacner as claimed is not an unexpected property because it has been well known in the art that presence of an enhancer in a trangenes tends to provide position independent expression (see Walters et al, PNAS 92:7125-7129, 1995). In addition, the position independent expression is not an unexpected finding, since the cited art clearly teaches that HS-40 enhancer element is capable of expressing in variety of cells types i.e. K562, MEL and HeLa cells.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633